# SUMMARY MINUTES

# GENERAL AND PLASTIC SURGERY DEVICES

# ADVISORY PANEL

## 59th Meeting

## OPEN SESSION

**July 17, 2001**

**Salons D & E, Grand Ballroom**
**Gaithersburg Hilton Hotel**
**620 Perry Parkway, Gaithersburg, Maryland**

**General and Plastic Surgery Devices Panel**
**July 17, 2001**

**Panel Participants**
Susan Galandiuk, M.D.
Acting Panel Chair

Joseph V. Boykin, Jr., M.D.
Voting Member

Phyllis Chang, M.D.
Voting Member

David L. DeMets, Ph.D.
Voting Member

Robert F. Diegelmann, Ph.D.
Temporary Voting Member

Mary H. McGrath, M.D., M.P.H., F.A.C.S.
Temporary Voting Member

E. Thomas Garman
Consumer Representative

Debera M. Brown
Industry Representative

**FDA Participants**
David Krause, Ph.D.
Executive Secretary, General and Plastic Surgery Devices Panel

Celia Witten, M.D., Ph.D.
Division Director, General, Restorative and Neurological Devices

Stephen P. Rhodes, M.A.
Branch Chief, Plastic and Reconstructive Surgery Devices Branch

Sam Arepalli, Ph.D.
Division of General and Restorative Devices

Roxolana Horbowyj, M.D.
Division of General and Restorative Devices

Mel Seidman
Division of Biostatistics

**OPEN SESSION**

At 10:31 a.m. **Panel Executive Chair David Krause, Ph.D.**, called the 59th meeting of the General and Plastic Surgery Devices Panel to order. After reading the conflict of interest statement into the record, he noted that waivers have been granted to Dr. David DeMets and Dr. Joseph Boykin so that they may participate in today's meeting. He deputized Dr. Mary McGrath and Dr. Robert Diegelmann as temporary voting members and Dr. Susan Galandiuk as acting panel chair.

**Dr. Celia Witten, Ph.D., M.D.**, of FDA, thanked Dr. Galandiuk for serving on this panel for the past three years and for acting as panel chair at today's meeting. She presented Dr. Galandiuk a letter of appreciation from Linda Suydam (Senior Associate Commissioner of FDA) and with a commemorative plaque. After introducing herself, **Acting Panel Chair Dr. Galandiuk** asked all the panel participants to introduce themselves.

**Stephen Rhodes, Branch Chief, Plastic and Reconstructive Surgery Devices**, updated the panel with a summary of the panel's recommendations and subsequent agency approvals for the past two years. He noted two personnel promotions; Jim Dillard had been promoted to the directorship of the Division of Cardiovascular and Respiratory Devices and Mark Melkerson had been promoted to the deputy directorship of the Division of General, Restorative and Neurological Devices. Mr. Rhodes closed by noting that the next meeting of the General and Plastic Surgery Devices Panel is tentatively scheduled for September 24 and 25, 2001.

## OPEN PUBLIC HEARING

No requests were heard from the audience to speak at the meeting.

## PREMARKET APPROVAL APPLICATION P010016: ORTEC INTERNATIONAL'S ORCEL™ COMPOSITE CULTURED SKIN

### Sponsor Presentation

**Dr. Costa Papastephanou** presented an historical background and the agenda for the presentation. The company is seeking approval for treatment with this device on split-thickness, donor-site wounds in burn patients.

**Dr. Mel Silberklang** described Ortec International's ORCEL™ Composite Cultured Skin ( henceforth CCS) as a preformed bovine collagen sponge containing two distinct types of cells, dermal fibroblasts and epidermal keratinocytes. He went on to describe the shipping package and the production process. He also discussed biocompatibility tests, safety testing of all cell types in the sponge, and product release tests. He concluded by stating that the CCS has been characterized and shown to be an open collagen matrix with actively dividing cells.

**Dr. John Griswold** reviewed clinical issues related to donor sites of burn patients. He juxtaposed potential problems of a donor site with an ideal donor site dressing. He stated that an ideal dressing would be easy to apply, would require minimal manipulation after placement, would reduce pain, speed healing and provide adequate cosmesis. He identified some dressings currently used on donor sites and went on to describe Biobrane-L, a commercially available dressing used as the control in this study.

Dr. Griswold summarized the CCS characteristics that mimic the characteristics that one would want in an ideal donor site dressing.

**Mr. Steven Peltier** outlined the pilot trial and the pivotal study. In the pivotal study investigators at separate sites treated 82 randomized patients who acted as their own controls in this matched pair designed study. Adhering to specific protocols, the investigators utilized planimetry, photography, and clinical examination to assess quality of donor site wound healing. Also, the time to healing was measured. During the study a matched set of donor sites would be created to obtain grafts for burn injuries. At the time of creation of the donor sites the patients would be randomized to treatment and evaluated at three days and then every 48 hours thereafter until healing was documented. Patients were only considered to be healed when 100% epithelialization was observed. Scar outcome was evaluated by two methods: the Vancouver Scar Scale and the Hamilton Scar Scale.

In his statistical analysis **Dr. Kazem Kazempour** studied data from scheduled patient visits up to six months after surgery and used 100% wound closure as an end point to the study. He concluded that CCS-treated donor site wounds healed faster than the control device-treated donor sites, that there was no significant difference in adverse events that occurred after treatment with CCS as compared to treatment with control, and that the administration of Oxandrolone to the study patients did not alter the study outcome.

With a brief slide presentation, **Dr. Paul Glat** compared clinical outcomes of CCS-treated patients with the outcomes of control device-treated patients. He explained

that CCS dissolves in three to five days and almost all wound sites were healed in 11 days. In Dr. Glat's opinion, CCS provided improved cosmesis over the control device.

**Dr. DeMets** questioned why the study stopped with 82 patients, why large gaps of time occurred in patient visits, the effect of Oxandrolone on the outcome of the investigation, and some statistical methods. The company representatives answered that stopping with 82 patients was purely a business decision. The patient visits adhered to a standard follow-up burn protocol, and Oxandrolone administration did not change the investigational outcome.

**Dr. Boykin** was concerned about pre-clinical testing for cellular retention, the time after the burn to graft harvest, whether the wound was dressed after the device backing was removed, and whether all investigators treated the wound site in the same, standardized manner. Dr. Boykin noted that patients less than 12 year of age and patients with burns over less than 20% total body surface area (TBSA) who were treated with CCS did not benefit significantly over similar patients receiving the control treatment.

The presenters noted that the time from burn to graft harvesting varied among the study patients. The clinical investigators employed standardized methods to treat the donor sites: with CCS they used a protocol and with Biobrane they followed the directions on the package insert.

The panel members had many questions for the presenters concerning the reason for Oxandrolone use, the treatment of donor wounds, the persistence of donor cells in the sponge, the assessment of the donor site for recropping, adverse events in the post-operative course and the masking of reviewers.

**FDA Presentation**

**Dr. Sam Arepalli** provided a brief device description, noted the indications for use, and listed the tests employed for biocompatibility testing in the collagen matrix and biocompatibility testing and toxicology of the cellular components. All of the tests revealed biocompatibility and no evidence of toxicity.

In addition to reviewing the CCS pilot study, **Dr. Roxolana Horbowyj** detailed the pivotal study outcomes. The main objectives of this 12-center study were safety and efficacy. Overall, median time to 100% healing for donor sites in burn patients was 12.0 days for CCS-treated donor sites and 17.0 days for control (Biobrane-L)-treated donor sites. Notable differences occurred in the outcomes at the various study sites with several covariate subgroups. While three centers showed little difference in healing time between the two devices, two centers found larger differences in the time to complete healing.

As the patients' age increased and as the burn size or TBSA increased, the difference in healing time between the devices increased. Treatment of patients with Oxandrolone increased the difference in healing time between the devices. In patients who received Oxandrolone (n = 30/82), donor sites treated with CCS had a median healing time = 13.0 days, while donor sites treated with control had a median healing time = 22.0 days. Conversely, in patients without Oxandrolone treatment (n= 52/82), donor sites treated with CCS had a median healing time = 12.0 days, while donor sites treated with control had a median healing time = 14.0 days. All 82 patients healed by 60 days after sustaining burns. Clinically, CCS demonstrated comparable outcomes with the

control when measuring itching, pain and scarring. Lack of data on recropped sites limits comparison statements.

In his statistical analysis, **Mr. Mel Seidman** agreed that the data confirmed the CCS device was stastically better than Biobrane-L in 100% wound closure. The upper confidence limit for any reported adverse event was less than 5%. Sixty four (78%) of the trial patients had at least one adverse event. Masking of the devices on the study photographs may have been impossible due to the distinct appearance and different application procedures of both devices. If the data of observer #1, which shows a wide divergence in healing rates between the devices, is removed from the trial findings, no statistical difference is noted in the device outcomes. The discrepancy between mean and median time to complete healing occurred, because the investigator changed the interval of the return visit to 30 days at the time the wound was 100% healed.

The study was stopped prematurely with an enrollment of 82 patients instead of the protocol sample size of 120 patients. Missing data is irreconcilable, since missing patients could have been treatment failures. Mr. Seidman has not reviewed the steroid information that was presented today.

**Dr. Arepalli** read the panel questions.

**Panel Clinical Review**

Commenting on the pivotal study, **Dr. Boykin** remarked that indications for efficacy need to be more focused, especially in patients over 12 years of age and with burns greater than 20 % TBSA. Grafts were not monitored with regard to thickness or time of harvest after burn occurrence. Labeling was needed to instruct clinicians on the

care of donor sites that become infected within the first week of device application. Further, labeling should state that the device not be used on infected sites.

**Dr. Boykin** posed two questions. Does treatment of 37% of the study patients with Oxandrolone bias the study? If these patients were removed from the study, would the study outcome be statistically significant?

**Dr. DeMets** raised several statistical issues that included patient noncompliance leading to bias, matched pair design, missing patients who are not random data points, subgroups that are too small and subsequently statistically insignificant, interactions with standard treatment and study outcome, and marked variation in results at different study sites.

The panel questioned the sponsor about the observed racial differences, use of Oxandrolone by center, differences of control results found in the study and the literature, and use of staples in both devices.

**Panel Questions**

There was consensus of the panel that the safety of the study device and the control device are comparable. The persistence of donor cells remains a concern.

The panel felt that CCS provided clinically significant results with some reservations concerning the handling of the control post-operatively, divergent results from the study centers, and the course of the donor cells in the wound site.

No definite clinically significant difference in scarring was observed between the CCS group and the control group. The panel members were consistent in their observations that the sponsor had not presented enough evidence to support claims of more rapid or improved healing.

The panel had several recommendations for labeling. No claim should be made that the device is superior to the control in patients less than 12 years old and in patients with burns covering less than 20% TBSA. The difference in results with and without Oxandrolone treatment should be noted. No statement should be made about recropping of wound sites. An exclusionary statement should list the types of patients not included in this study. A cautionary statement should advise how to handle an infected donor site.

**OPEN PUBLIC HEARING**

No one came forward to speak from the audience.

**Panel Executive Secretary David Krause** read the voting rules and options. A motion was made and seconded to recommend the device as approvable with conditions. The panel listed those conditions found in the previous discussion on labeling and added a statement that the device does not provide more rapid healing than existing products. In addition, they recommended a follow-up histology study to determine donor cell survival in the device. The motion passed unanimously.

**Acting Panel Chair Dr. Susan Galandiuk** thanked all the participants at the meeting and adjourned the meeting at 3:25 p.m.

I certify that I attended the Open Session of the General and Plastic Surgery Devices Panel Meeting on July 17, 2001, and that this summary accurately reflects what transpired.

David Krause, Ph.D.
Executive Secretary

I approve the minutes of the meeting as recorded in this summary.

Susan Galandiuk, M.D.
Acting Panel Chair

Summary minutes prepared by Lynn Blei
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Summary minutes edited by David Krause
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10/17/01